Katie J.L. Scott (Cal. Bar No. 233171)
Email address: katie.scott@arnoldporter.com
Joshua Seitz (Cal Bar No. 325236)
Email address: joshua.seitz@arnoldporter.com
ARNOLD & PORTER KAYE SCHOLER LLP
3000 El Camino Real
Building 5, Suite 500
Palo Alto, California 94306
Telephone: (650) 319-4500
Facsimile: (650) 319-4700

Matthew M. Wolf (admitted *pro hac vice*)
matthew.wolf@arnoldporter.com
Jennifer Sklenar* (Cal. Bar. No. 200434)
jennifer.sklenar@arnoldporter.com
ARNOLD & PORTER KAYE SCHOLER LLP
601 Massachusetts Ave, NW
Washington, DC 20001-3743
Telephone: (202) 942-5000
Facsimile: (202) 942-5999
*Admitted in NY and CA only; practice limited to matters before federal courts and federal agencies

Attorneys for Defendants
BGI AMERICAS CORP., MGI TECH CO., LTD., MGI AMERICAS, INC., and COMPLETE GENOMICS, INC.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
SAN FRANCISCO DIVISION

ILLUMINA, INC., and ILLUMINA CAMBRIDGE LTD.,

Plaintiffs,

v.

BGI GENOMICS CO., LTD., BGI AMERICAS CORP., MGI TECH CO., LTD., MGI AMERICAS, INC. and COMPLETE GENOMICS, INC.

Defendants.

Case No. 3:19-cv-03770-WHO
Case No. 3:20-cv-01465-WHO

DEFENDANTS' CORRECTED OPPOSITION TO PLAINTIFFS' MOTIONS FOR PRELIMINARY INJUNCTION

Date: May 11, 2020
Time: 2:00pm
Location: Courtroom 2, 17th Floor

Hon. William H. Orrick

TABLE OF CONTENTS

I. FACTUAL BACKGROUND 2

II. THIS COURT SHOULD DENY ILLUMINA'S MOTIONS 4

A. Illumina Is Not Likely to Succeed on The Merits 4

1. Illumina Has Not Shown Likely Infringement By CoolMPS 5

2. There Is At Least A Substantial Question Of Invalidity 6

a. The Asserted '444/'973 Claims Are Not Enabled 6

b. The Asserted '444/'973 Claims are Anticipated or Obvious 17

c. Claim 3 of the '444 Patent is anticipated 18

d. Claim 3 of the '444 Patent is obvious 20

e. Claim 13 of the '973 Patent is obvious 22

f. The Asserted '025/'200/'537 Claims Are Not Enabled 23

B. Illumina Will Not Suffer Irreparable Harm 23

1. Monetary Damages are Adequate to Compensate for Any Alleged Harm. 26

2. No Causal Nexus Between Alleged Harm and Alleged Infringement. 27

C. Equity Weighs Heavily Against A Preliminary Injunction 27

D. The Public Interest Would Be Disserved by A Preliminary Injunction 28

III. THE SCOPE OF ILLUMINA'S PROPOSED INJUNCTION IS OVERBROAD. 30

IV. CONCLUSION 30

TABLE OF AUTHORITIES

Cases

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.,
759 F.3d 1285 (Fed. Cir. 2014) 19

Altana Pharma AG v. Teva Pharm. USA, Inc.,
566 F.3d 999 (Fed. Cir. 2009) 7

ALZA Corp. v. Andrx Pharm., LLC,
603 F.3d 935 (Fed. Cir. 2010) 10

Amazon.com, Inc. v. Barnesandnoble.com, Inc.,
239 F.3d 1343 (Fed. Cir. 2001) 5

Amgen Inc. v. Sandoz Inc.,
923 F.3d 1023 (Fed. Cir.),
reh'g granted, opinion modified, 776 F. App'x 707 (Fed. Cir. 2019) 6

Apple Inc. v. Samsung Elecs. Co.,
695 F.3d 1370 (Fed. Cir. 2012) 30

Apple, Inc. v. Samsung Elec. Co., Ltd.,
678 F.3d 1314 (Fed. Cir. 2012) 26

Automated Merch. Sys., Inc. v. Crane Co.,
357 F. App'x 297 (Fed. Cir. 2009) 26, 28

Beats Elecs., LLC v. Fanny Wang Headphone Co., Inc.,
No. C-10-5680 MMC, 2011 WL 31198 (N.D. Cal. Jan. 5, 2011) 26

Brown v. 3M,
265 F.3d 1349 (Fed. Cir. 2001) 20

Conceptus, Inc. v. Hologic, Inc.,
No. 09-02280 (WHA), 2012 WL 44064 (N.D. Cal. Jan. 9, 2012) 32

Cordis Corp. v. Bos. Sci. Corp.,
99 F. App'x 928 (Fed. Cir. 2004) 32

Docusign, Inc. v. Sertifi, Inc.,
468 F. Supp. 2d 1305 (W.D. Wash. 2006) 7

eBay, Inc. v. MercExchange, LLC,
547 U.S. 388 (2006) 29

Entegris, Inc. v. Pall Corp.,
490 F.3d 1340 (Fed. Cir. 2007) 5

Enzo Biochem, Inc. v. Calgene, Inc.,
188 F.3d 1362 (Fed. Cir. 1999) 8

Enzo Life Sci. v. Roche Molecular Sys., Inc.,
928 F.3d 1340 (Fed. Cir. 2019) 8, 17, 19

Fujifilm Corp. v. Motorola Mobility LLC,
No. 12-CV-03587-WHO, 2015 WL 757575 (N.D. Cal. Feb. 20, 2015) 22

Helmsderfer v. Bobrick Washroom Equip., Inc.,
527 F.3d 1379 (Fed. Cir. 2008) 6

Hutchins v. Zoll Med. Corp.,
492 F.3d 1377 (Fed. Cir. 2007) 6

Hybritech Inc. v. Abbott Labs.,
849 F.2d 1446 (Fed. Cir. 1988) 32

Idenix Pharm., LLC v. Gilead Sci. Inc.
941 F.3d 1149 (Fed. Cir. 2019) 8, 17, 19

Leapfrog Enters., Inc. v. Fisher-Price, Inc.,
485 F.3d 1157 (Fed. Cir. 2007) 6

LEGO A/S v. ZURU Inc.,
No. 2019-2122, 2020 WL 229874 (Fed. Cir. Jan. 15, 2020) 29

MagSil Corp. v. Hitachi Glob. Storage Techs.,
687 F.3d 1377 (Fed. Cir. 2012) 8, 19

Mass. Inst. of Tech. v. Shire Pharm., Inc.,
839 F.3d 1111 (Fed. Cir. 2016) 22

Mike's Train House, Inc. v. Broadway Ltd. Imports, LLC,
708 F. Supp. 2d 527 (D. Md. 2010) 28

Millipore Corp. v. W.L. Gore & Assocs., Inc.,
No. CIV.A. 11-1453 ES, 2011 WL 5513193 (D.N.J. Nov. 9, 2011) 7

MMJK, Inc. v. Ultimate Blackjack Tour LLC,
513 F. Supp. 2d 1150 (N.D. Cal. 2007) 27, 30

Monsanto Co. v. Syngenta Seeds, Inc.,
503 F.3d 1352 (Fed. Cir. 2007) 10

NantKwest, Inc. v. Lee,
686 F. App'x 864 (Fed. Cir. 2017) 20

New Eng. Braiding Co. v. A.W. Chesterton Co.,
70 F.2d 878 (Fed. Cir. 1992) 7

Novozymes A/S v. DuPont Nutrition Biosciences APS,
723 F.3d 1336 (Fed. Cir. 2013) 19

NYKO Techs. Inc v. Energizer Holdings Inc.,
No. CV 12-03001 GAF (VBKx), 2012 WL 12882885 (C.D. Cal. June 1, 2012) 33

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005) 21

Schering Corp. v. Geneva Pharm.,
339 F.3d 1373 (Fed. Cir. 2003) 12

Sciele Pharma Inc. v. Lupin Ltd.,
684 F.3d 1253 (Fed. Cir. 2012) 20

Standard Innovation Corp. v. Lelo (Shanghai) Trading Co.,
No. 15-cv-04858-BLF, 2015 WL 6828317 (N.D. Cal. Nov. 6, 2015) 27

Takeda Pharm. Co., Ltd v. Handa Pharm., LLC,
No. C-11-00840 JCS, 2013 WL 9853725 (N.D. Cal. Oct. 17, 2013) 12

Winter v. Natural Resources Defense Council, Inc.,
555 U.S. 7 (2008) 4, 26

Wyeth v. Abbott Labs.,
720 F.3d 1380 (Fed. Cir. 2013) 8, 18, 19

Statutes

35 U.S.C. § 102 ..... 2, 19
35 U.S.C. § 103 2
35 U.S.C. § 112 1
35 U.S.C. § 112(a) 7

TABLE OF ABBREVIATIONS

Abbreviation	Term
-3770 D.N.	Docket entries from Case No. 3:19-cv-03770-WHO
-1465 D.N.	Docket entries from Case No. 3:20-cv-01465-WHO
NGS	next generation sequencing
WGS	whole genome sequencing
The ’444 Patent	U.S. Patent No. 7,541,444
The ’937 Patent	U.S. Patent No. 7,771,973
The ’025 Patent	U.S. Patent No. 10,480,025
The ’537 Patent	U.S. Patent No. 7,566,537
The ‘200 Patent	U.S. Patent No. 9,410,200
MGI Americas	MGI Americas, Inc.
CGI	Complete Genomics, Inc.
MGI Tech	MGI Tech Co., Ltd.
BGI	BGI Group
KOL	key opinion leader
SBS	sequencing-by-synthesis
PTO	U.S. Patent & Trademark Office
PCT	Patent Cooperation Treaty
PI	Preliminary Injunction
Illumina	Illumina, Inc., and Illumina Cambridge Ltd.

MGI Americas is preparing to launch next-generation sequencing technology, including chemistry called "CoolMPS," which was invented and developed through years of hard work by a team of chemists in its San Jose, California facility. One of the many ways CoolMPS differs from prior technology is that it uses a revolutionary antibody-based chemistry that avoids DNA "scars," which accumulate with the labels/linkers used in traditional sequencing methods (including Illumina's methods) and affect the accuracy of subsequent reads or sequence identifications. Instead, CoolMPS introduces ***un***labeled nucleotides and fluorescently labeled antibodies in its sequencing process to recognize each nucleotide after it is incorporated. This novel technology is poised to have long term benefits in DNA sequencing, both because scarless natural bases provide for more accurate and longer reads of DNA sequences and the technology is less costly.

No doubt threatened by a new market entrant with superior products, Illumina—a company that has tried to maintain its stranglehold over the industry for nearly two decades—seeks the extraordinary relief of a preliminary injunction. Illumina is not only trying to enjoin the sale of CoolMPS but also its use in internal research, as well as any use of StandardMPS chemistry that Defendants currently have no intention of selling. Illumina's Motions should be seen for what they are—a monopolist's overreach and misuse of the patent system. Each of the preliminary injunction factors militates against Illumina's Motions, as shown below and in the accompanying declarations.

First, Illumina cannot establish a likelihood of success on the merits. It fails to address issues of claim construction or show that CoolMPS likely meets all limitations of any patent claim. All of the asserted claims are also grossly overbroad and, given the meager disclosure in the specification and unpredictable nature of the art, invalid under 35 U.S.C. § 112 for lack of enablement. In short, the technique of using ***un***labeled nucleotides and fluorescently labeled antibodies is Defendants' innovation, not Illumina's, and is certainly not enabled by the specifications at issue. Moreover, prior art embodiments of the asserted claims, distinct from the accused CoolMPS, invalidate the asserted claims under 35 U.S.C. §§ 102 or 103.[1]

Second, Illumina cannot show that it will suffer irreparable harm, or that monetary damages are inadequate, if the Motions are denied. Given its advanced technology and lower price point,

[1] Given page and time limits, Defendants focus only on certain defenses herein.

CoolMPS will vastly expand the market by making population-scale DNA sequencing affordable and ushering in a new era where personalized medicine is the norm. But, CoolMPS will likely take years to get enough market traction to make even a small dent in Illumina's dominant market presence due to the barriers to entry, including Illumina's contracting practices designed to lock customers into long term and near-exclusive use of Illumina's products. While there may be some overlap in MGI Americas' sales with Illumina's current customers, such overlap is estimated to be minimal pending trial and would ultimately be compensable by monetary damages, if necessary.

Third, the balance of hardships favors Defendants. Defendants have invested at least [redacted] in developing its novel CoolMPS technology and employs [redacted] researchers in its San Jose facility, whose jobs will be at risk should a preliminary injunction be entered. In addition, MGI Americas' entrance in the U.S. market is expected to substantially expand the market, rather than convert market share from Illumina. The balance of harms also favors Defendants because they too have infringement claims against Illumina, and it would be highly unfair to enjoin MGI Americas' launch while Illumina freely impinges upon Defendants' patent rights.

Fourth, the public interest favors denial of the Motions. As the proverbial 800 pound gorilla with at least a 90% share of the domestic high throughput DNA sequencing market, Illumina has shown that it will stop at no cost to squelch competition and innovation to keep its prices for WGS artificially high, which slows the important genomic research that advances healthcare. Plainly, the public will benefit from expanded access of health researchers to improved and significantly different DNA sequencing technology at lower prices, which CoolMPS would provide.

I. FACTUAL BACKGROUND

The Defendants: CGI was founded in San Jose, California in 2005 and became part of BGI in 2013 and MGI Tech. (the instruments manufacturing business of BGI) in 2018. Ex. D1.[2] MGI Americas is the commercial arm of MGI Tech. that focuses on the Americas. BGI has its origins as a research institute and has an enduring commitment to research and development. Ex. D2. BGI currently focuses on several facets of biotechnology, including genome sequencing, proteomics, and diagnostics. *Id.*; Ex. D3. Through BGI's dedicated research divisions and not-for-profit affiliates, it

[2] All "Ex. D_" references are to the exhibits of the April 10, 2020, declaration of Katie J.L. Scott.

has significantly contributed to the development of the field. As but one recent example, BGI quickly developed a coronavirus test kit and has donated more than 132,500 kits to hospitals, local disease centers, and laboratories around the globe. Ex. D4, D5, D6. BGI also partners and collaborates with global institutions and international research centers. As one example, it has a long-standing partnership with the Bill & Melinda Gates Foundation focused on projects and strategies to apply genomic tools to improve global health and agricultural development, particularly in the developing world. Ex. D7. BGI has also collaborated with numerous companies, universities, and not-for-profit organizations, including Merck, AstraZeneca, University of Copenhagen, Karolinska Institute, United Nations Development Programme, International Society for Biological and Environmental Repositories, and the International Cancer Genome Consortium. *See, e.g.*, Exs. D8, D9, D10, D11, D12.

CGI's Development of Sequencing Technology: CGI, along with other companies in the BGI corporate family, have developed cutting edge sequencing technologies, which MGI Americas intends to sell in the U.S. *See, e.g.*, Exs. D13, D14, D15. For example, the DNBseq™ platform combines several innovative technologies to provide massively parallel sequencing capabilities. Ex. D14. Unlike Illumina's technology, the DNBseq™ platform is PCR-free and uses arrays of DNA nanoballs that are generated by rolling circle replication, which has the advantage of reduced errors during amplification as compared to Illumina's approach. *Id.* This platform provides billions of sequencing reads at relatively low cost and enables a multitude of genomic applications. *Id.* At least two of Defendants' patented sequencing technologies are infringed by Illumina, including the two-color sequencing and high density patterned array technologies, and are the subject of CGI's infringement claims against Illumina in this Court and in the District of Delaware.[3]

Particularly relevant to the second PI motion is Defendants' CoolMPS chemistry, which MGI Americas intends to launch for use with its sequencing instruments. CoolMPS is an innovative, antibody-based, chemistry that avoids the DNA scars that accumulate with the labeled linkers used in traditional sequencing methods, like Illumina's, and negatively affect the accuracy of subsequent reads. Smith ¶¶48-50, 108-109; Ex. D16 at Abstract and CGI000042776. In contrast to

[3] *Illumina, Inc. et al v. BGI Genomics Co., Ltd et al.*, 3-19-cv-03770 D.I. 94 at ECF 37-67 (N.D. Cal. Feb. 24, 2020); *Complete Genomics, Inc. v. Illumina, Inc.*, 1-19-cv-00970 D.I. 7 (D. Del.).

Illumina's approach, CoolMPS introduces ***un***labeled nucleotides for incorporation to the DNA being sequenced and then uses innovative fluorescently labeled antibodies to recognize the incorporated bases. *Id.* at Abstract. This novel chemistry is particularly beneficial in applications that require low DNA input and high throughput sequencing applications (including WGS), which require high quality data and sensitivity, long read lengths, and efficient, affordable reagents. *Id.*

Defendants have also developed more traditional chemistry — referred to as "StandardMPS" —that MGI Americas does ***not*** currently intend to launch commercially in the U.S. Instead, MGI Americas plans to provide StandardMPS reagent kits when necessary for KOLs to validate new applications or for comparative research purposes.

Illumina: Illumina has an estimated 90% market share in the domestic sequencing industry. Ex. D17 ¶¶1, 34, 41, 51. It has tried to maintain or increase that market share by squelching competition through aggressive patent litigation tactics and acquisitions. *Id.* ¶¶7-9; Ex. D18. The Federal Trade Commission recently recognized that Illumina is a "monopolist" who tried to "unlawfully maintain" its monopoly over next generation DNA sequencing systems through a proposed $1.2 billion purchase of Pacific Biosystems of California. Ex. D19. After multiple international antitrust authorities challenged its proposed acquisition, Illumina was forced to relent. *Id.*; Ex. D49 at 227:6-15. Illumina's monopoly has led it to be complacent in terms of offering new innovations and competitive prices—all of which pose significant harm to U.S. consumers, government healthcare, and research payors, while stifling innovation in this critical field.

II. THIS COURT SHOULD DENY ILLUMINA'S MOTIONS

"A preliminary injunction is an extraordinary remedy never awarded as of right." *Winter v. Natural Resources Defense Council, Inc.*, 555 U.S. 7, 25 (2008). "The grant or denial of a preliminary injunction . . . is within the sound discretion of the district court." *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001).

A. Illumina Is Not Likely to Succeed on The Merits

Illumina "bears the burden of establishing a likelihood of success on the merits with respect to the patent's validity." *Entegris, Inc. v. Pall Corp.*, 490 F.3d 1340, 1351 (Fed. Cir. 2007). Illumina asserts (1) claim 13 of the '973 Patent and claim 3 of the '444 Patent against the CoolMPS

and StandardMPS products, and (2) claims 1-8 of the '025 Patent, claims 1-2, 4-12, and 14-19 of the '200 Patent, and claims 1-6 of the '537 Patent against StandardMPS.[4]

1. Illumina Has Not Shown Likely Infringement By CoolMPS

Illumina has failed to show that there is likely literal infringement of the claims asserted against CoolMPS—*i.e.*, claim 13 of the '973 Patent and claim 3 of the '444 Patent. Although Illumina identifies the required two step process for determining infringement (claim construction and application of the construed claims to the accused product/method), its memorandum contains no analysis of either issue. Instead, it makes liberal reference to Dr. Burgess's Declaration but he also fails to provide any real claim construction (3:20-cv-01465 Dkt. No. 13 ¶48) or complete analysis of whether the claims cover CoolMPS. This failure may be explained by fact that an in-depth analysis of the claims would reveal additional invalidity issues (such as indefiniteness) but, whatever the reason, a party is not entitled to extraordinary relief on such a shoddy record.

For claim 13 of the '973 Patent, Dr. Burgess fails to address the meaning of the claim terms that he is applying, most notably the last limitation of independent claim 1, "wherein the blocking group is removed prior to ***introduction*** of the next complementary nucleotide." In his analysis, he simply assumes that the term "introduction" means "incorporation" (*id.* ¶61)[5], but "***incorporation***" and "***introduction***" are two different claim terms and he provides no analysis whatsoever as to why they should be interpreted to mean the same thing (*see id.* ¶48). *See Amgen Inc. v. Sandoz Inc.*, 923 F.3d 1023, 1031 (Fed. Cir.), *reh'g granted, opinion modified*, 776 F. App'x 707 (Fed. Cir. 2019) ("Our precedent instructs that different claim terms are presumed to have different meanings.") (quoting *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1382 (Fed. Cir. 2008)). The distinction is critical, because CoolMPS can introduce the next batch of nucleotides to the reaction mixture ***before*** removal of the blocking group (D16 at 5-7), which is contrary to the actual claim language. Because Dr. Burgess' opinion is based on language not found in the asserted claim, he fails to show that CoolMPS likely meets every requirement of claim 13.

[4] The '444 and '973 Patents share the same specification (*i.e.*, the text and figures other than the claims). The '537, '200, and '025 Patents share a different and earlier specification.

[5] *See also*, Case No. 3:20-cv-01465 Dkt. No. 13, ¶ 64 ("[T]hese labelled nucleotides require cleavage of the blocking group prior to ***incorporation*** of the next nucleotide.").

For dependent claim 3 of the '444 Patent, Dr. Burgess waves off various requirements of its independent (claim 1) as inapplicable with no real analysis other than his assertion that Illumina is "solely asserting claim 3, which does not require R" structures." *Id.* ¶42. But he overlooks the fact that claim 3 depends from claim 1, and claim 1's limitations, including the last clause "wherein said molecule may be reacted to yield an intermediate in which each R" is exchanged for H, which intermediate dissociates under aqueous conditions to afford a molecule with a free 3'OH . . ." are requirements of claim 3 as a matter of law. *See Hutchins v. Zoll Med. Corp.*, 492 F.3d 1377, 1382 (Fed. Cir. 2007); *see also Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1160 (Fed. Cir. 2007) (claims should not be construed to render claim language superfluous). He also overlooks the inconsistency between the specification and file history, which alternatively describe azidomethyl groups as including and excluding R" groups, respectively. *See* Ex. D38 at 2. Because Dr. Burgess has utterly failed to address multiple requirements of claim 1, Illumina has failed to carry its burden of showing likely infringement. *See Millipore Corp. v. W.L. Gore & Assocs., Inc.*, No. CIV.A. 11-1453 ES, 2011 WL 5513193, at *11 (D.N.J. Nov. 9, 2011); *Docusign, Inc. v. Sertifi, Inc.*, 468 F. Supp. 2d 1305, 1308–09 (W.D. Wash. 2006).

2. There Is At Least A Substantial Question Of Invalidity

At this stage, Defendants need only raise a "substantial question of invalidity," which is detailed below and in the Sutherland declaration, to rebut any likelihood of success. *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1005-06 (Fed. Cir. 2009). Illumina cannot carry its burden of showing that these "defense[s] lack[] substantial merit." *New Eng. Braiding Co. v. A.W. Chesterton Co.*, 970 F.2d 878, 882–83 (Fed. Cir. 1992).

***a.* The Asserted '444/'973 Claims Are Not Enabled**

Under 35 U.S.C. § 112(a), a patent's specification must enable those skilled in the art to ***make and use the full scope*** of the claimed invention without undue experimentation as of the patent filing date.[6] (August 2003 for the '973 and '444 Patents). *Wyeth v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Enablement is an "important doctrine [that] prevents both inadequate

[6] Illumina has asserted August 23, 2002 as the priority date for the '537, '200, and '025 Patents, but has not committed to a priority date for the '444 and '973 Patents. For purposes herein, Defendants use August 22, 2003 as the priority date for those patents, but an earlier date would not impact the arguments other than to strengthen the enablement challenge. *See* Sutherland ¶¶63-66, 85, 91, 96.

disclosure of an invention and overbroad claiming that might otherwise attempt to cover more than was actually invented." *MagSil Corp. v. Hitachi Glob. Storage Techs.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012). Whether a patent satisfies the enablement requirement "is a question of law based on underlying facts." *Id*. at 1380. In examining this defense, courts typically consider the scope of the claims, the disclosure of the specification, the predictability of the field, and the amount of experimentation. *See Wyeth*, 928 F.3d at 1384; *Enzo Life Sci. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340 (Fed. Cir. 2019) (cert. denied); *Idenix Pharm., LLC v. Gilead Sci. Inc*. 941 F.3d 1149 (Fed. Cir. 2019).[7]

As detailed below, claim 13 of the '973 Patent is directed to a method of determining the sequence of a target polynucleotide, covering the potential incorporation of millions of 3'-O-azidomethyl blocked nucleotides by millions of enzymes with unlimited sequencing read length using labeled or unlabeled nucleotides. Yet, the specification of the '973 Patent does not describe a single working example of such sequence determination. Given the breadth of the claim, the lack of meaningful guidance in the specification, the nascent field of sequencing by 3' blocked nucleotides at the time of the alleged invention, practicing the full scope of claim 13 of the '973 Patent would have required systematic trial-and-error process that constitutes undue experimentation.

Claim 3 of the '444 Patent is a product claim that covers millions of 3'-O-azidomethyl blocked nucleotides, including any detectable label via any linker attached to any base position of the nucleotide. The specification of the '444 Patent only discloses the synthesis of four 3'-O-azidomethyl blocked nucleotides with a single detectable label and a single linker attached to a single base position. Given the great difficulty in making structurally diverse 3'-O-azidomethyl blocked nucleotides with suitable linkers and labels at the time of alleged invention, practicing the full scope of claim 3 of the '444 Patent would have required undue experimentation.

The claim scope is extremely broad. Claim 13 of the '973 Patent and claim 3 of the '444 Patent by virtue of their respective independent claims recite a "nucleotide." '973 Patent at 86:26; '444 Patent at 85:65. Despite limiting the 3'-OH position of the nucleotide to an "azidomethyl"

[7] While the *Wands* factors may be considered in an enablement inquiry, an analysis of all eight factors is not required. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999).

("3'-O-azidomethyl") blocking group, claim 13 of the '973 Patent and claim 3 of the '444 Patent each cover at least millions of 3'-O-azidomethyl blocked compounds. *See* Sutherland ¶¶28-41.

First, the specification of the '444 and '973 Patents defines "nucleotide" as "consisting of a nitrogenous base, a sugar, and one or more phosphate groups" and further defines that a "nucleotide" as encompassing a "derivative" and "analogue" of the nucleotide and a "modified" nucleotides. '444 Patent at 14:11-12, 14:33-39, 14: 51-53 ("'Derivative,' 'analog" and "modified' as used herein, may be used interchangeably, and are encompassed by the terms 'nucleotides'…defined herein"). The specification then defines a "derivative" or "analogue" as a "compound or molecule whose core structure is the same as, or closely resembles that of, a parent compound [*i.e.*, a nucleotide]…." '444 Patent at 14:29-39. Because the core structure of a nucleotide includes base and sugar moieties, a nucleotide derivative or analogue would include modifications at the base moiety (base analogs) and sugar moiety (sugar analogs).[8] There were thousands of sugar analogs (excluding modifications at the 3' position)[9] and base analogs known in August 2003. The specification of the '444 and '973 Patents refers to two references, which alone identify hundreds of sugar analogs (excluding modifications at the 3' position) and base analogs known as of 1990. Ex. D21; Ex. D22; *See* Sutherland ¶¶29-30.

Second, as discussed above, the scope of "nucleotide" in claim 3 of the '444 Patent and claim 13 of the '973 Patent also includes a nucleotide "derivative," a nucleotide "analog," and "modified" nucleotide. As used in these patents, a nucleotide "derivative," a nucleotide "analog," and/or "modified" nucleotide encompasses a nucleotide where a detectable label is attached a base position of the nucleotide.[10] *E.g.*, '444 Patent at 16:5-6 ("The modified nucleotide of the invention

[8] As detailed below, Illumina has used "nucleotide" and "nucleoside" interchangeably in the Asserted Patents. A derivative or analog of a nucleotide also includes modifications at the phosphate moiety of a nucleotide. Nevertheless, the number of sugar and base analogs alone, without including phosphate analogs, already demonstrates the incredible breadth of claim 3 of the '444 Patent and claim 13 of the '973 Patent.

[9] A modification at the 3' position is excluded because claim 3 of the '444 Patent and claim 13 of the '973 Patent require a 3'-O-azidomethyl group.

[10] In other words, the "nucleotide" in claim 3 of the '444 Patent and claim 13 of the '973 Patent could be either labeled or unlabeled nucleotides. Illumina's infringement contentions also confirm that it is construing the limitation "monitoring the sequential incorporation of complementary nucleotides" of the '973 Patent such that it encompasses monitoring techniques that use both labeled and unlabeled nucleotides. 3:20-cv-01465 Dkt. No. 1-4 at 1-2. Both the labeled and unlabeled

(Footnote Cont'd on Following Page)

may use a cleavable linker to attach the label to the nucleotide."); 86:44-49.[11] The specification teaches that detectable labels include "fluorescent labels," "microparticles," "quantum dots," "gold nanoparticles," "microbeads," and "multi-component labels." '444 Patent at 15:49-64. In the 2002-2003 time frame, hundreds of such detectable labels were known. *See* Sutherland ¶¶31-32.

Third, similar to a detectable label discussed above, claim 3 of the '444 Patent and claim 13 of the '973 Patent also cover a nucleotide where a linker is attached to a base position of the nucleotide because the detectable label is attached to the nucleotide through the linker. '444 Patent at Fig. 3; 16:5-6, 17:12-18; 86:44-49. The specification teaches that suitable linkers include "disulfide linkers," "acid labile linkers," "electrophilically cleavable linkers," "nucleophilically cleavable linkers," "photocleavable linkers," and "cleavage under reductive conditions, oxidative conditions, cleavage via use of safety-catch linkers, and cleavage by elimination mechanisms." '444 Patent at 16:64-17:15; 17:34-42. In the 2002-2003 time frame, hundreds of cleavable or a non-cleavable linkers were known. *See* Sutherland ¶¶33-41.

In sum, the term "nucleotide" in the asserted'444 and'973 Patent claims includes at least a base analog, a sugar analog (other than modifications at the 3' position), and a modified nucleotide with any detectable label via any linker at any base position. Even a conservative estimate of this broad scope of "nucleotide" encompasses millions of different 3'-O-azidomethyl nucleotides with different combinations of sugar and base analogs, detectable labels, and linkers. *See* Sutherland ¶41. Indeed, Dr. Burgess admitted that "[a]n infinite number of nucleotide derivatives could be imagined [] even with azidomethyl only as a 3' protected group." Ex. D23 at 103:9-11.

Further, claim 13 of the '973 Patent is directed to a method for "determining the sequence of target single-stranded polynucleotide, comprising monitoring the sequential incorporation of complementary nucleotides, wherein at least one incorporation is of a nucleotide having a removable" 3'-O-azidomethyl blocking group. Thus, while claim 13 requires "sequential

---

embodiments must satisfy the enablement requirement. *See ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 938 (Fed. Cir. 2010) (Full scope of "dosage form" required enablement of both osmotic and non-osmotic dosage forms); *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1361 (Fed. Cir. 2007) (Full scope of "plant cell" required enablement of both dicots and monocots.).

[11] In addition to being a "modified" nucleotide, a base-labeled (via a cleavable linker) nucleotide is also a nucleotide "derivative" and "analog," because "derivative" and "analog" are defined as including "synthetic nucleotide derivative having modified base moieties." '444 Patent at 14:41-44.

incorporation" and "at least one incorporation" of a 3'-O-azidomethyl blocked nucleotide,[12] it does not restrict the sequencing length, *i.e.*, the read length, of the target polynucleotide. *See* Sutherland ¶47.

Moreover, the term "incorporation" in claim 13 of the '973 Patent includes at least enzymatic incorporation, such as by a polymerase. '973 Patent at 5:56-68. The claimed method encompasses the use of any enzyme—naturally occurring (wild type) or generally engineered (mutants)—to achieve incorporation. '973 Patent at 18:59-19:10. There are at least millions of wild type and engineered enzymes available for potential incorporation of 3'-O-azidomethyl blocked nucleotides. *See* Sutherland ¶¶42-46. Indeed, Dr. Burgess admitted that "an infinite number of polymerases could be imagined by making mutants …to natural polymerases." Ex. D23 at 103:11-13.

The disclosures of the specification are insufficient. ***First***, despite claiming millions of 3'-O-azidomethyl blocked nucleotides, the specification of the '444 Patent describes the synthesis of only eight such nucleotides:

- a 3'-O-azidomethyl blocked uridine triphosphate modified at a base position with a Cy-3 fluorescent label via a disulfide linker (structure 6) and its synthetic precursor without the label or the disulfide linker (structure 5) ('444 Patent at 27:30-58, 24:20-32)
- a 3'-O-azidomethyl blocked cytidine triphosphate modified at a base position with Alexa Fluor fluorescent label via a disulfide linker (structure 18) and its synthetic precursor without the label or the disulfide linker (structure 17) ('444 Patent at 41:30-53, 38:35-50)
- a 3'-O-azidomethyl blocked guanosine triphosphate modified at a base position with a Cy-3 fluorescent label via a disulfide linker (structure 24) and its synthetic precursor without the label or the disulfide linker (structure 23) ('444 Patent at 49:1-29, 47:15-32)
- a 3'-O-azidomethyl blocked adenosine triphosphate modified at a base position with a Cy-3 fluorescent label via a disulfide linker (structure 32) and its synthetic precursor without the label or the disulfide linker (structure 31) ('444 Patent at 57:30-54, 56:1-20)

And, the above eight compounds actually reflect (1) only two fluorescent labels (Cy-3 and Alexa Fluor) and one linker (disulfide linker) at one base position and (2) for each nucleotide, a single label and a single linker attached to a single base position. *See* Sutherland ¶51.

Second, the specification of the '973 and '444 Patents describes no working example of using 3'-O-azidomethyl nucleotides in actual sequencing of a polynucleotide as recited in claim 13

[12] The claim scope also encompasses incorporation using a mixture of four unlabeled 3'-O-azidomethyl nucleotides and monitoring sequential incorporation of these unlabeled nucleotides.

of the '973 Patent. *See* Sutherland ¶¶52-57. The only purported example of using 3'-O-azidomethyl nucleotides spans less than a column and uses the present tense, indicating a prophetic example, not an actual example.[13] *See* '973 Patent at 59:24-60:3, 59:26-27 ("The reaction ***can be*** performed…."); 42-44 ("This solution ***is*** then added to the beads and mixed thoroughly and incubated at 65 °C. for 10-15 minutes.") (emphases added); *see Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1376 n.1 (Fed. Cir. 2003) ("Prophetic examples are set forth in the present tense to indicate that they were not carried out."); *Takeda Pharm. Co., Ltd v. Handa Pharm., LLC*, No. C-11-00840 JCS, 2013 WL 9853725, at *72 (N.D. Cal. Oct. 17, 2013) ("[A]ll of the examples . . . are set forth in present tense, indicating that they are 'prophetic' and were not carried out.").

In any event, while the use of a "hairpin DNA" as a target DNA is described in this example, the specification does not provide the length or sequence of such "hairpin DNA." '973 Patent at 59:25. Thus, there is no way to discern whether the determination of the sequence of the "hairpin DNA" was actually successful. *See* Sutherland ¶53. Even for the purported incorporation of 3'-O-azidomethyl nucleotides in this example, the specification merely shows two gels without describing the experimental conditions or measurements demonstrating whether the incorporation of the correct nucleotide was indeed accomplished, and if so, the efficiency of the purported incorporation. '937 Patent at Figs. 5-6, 59:24-60:3; Sutherland ¶¶54-55, 57. Even if sequencing of "hairpin DNA" were described, there is no disclosure of determining the sequence of any other target polynucleotide. *See* Sutherland ¶56.

Third, the specification provides only generalized statements on how to make and use 3'-O-azidomethyl blocked nucleotides. *See* Sutherland ¶¶59-62. Indeed, other than the 3'-O-azidomethyl protected nucleotides with a single label (Cy3 or Alexa Fluor) and a single disulfide linker at one base position, the specification does not describe how to synthesize 3'-O-azidomethyl protected nucleotides with any other labels or linkers attached to any other base positions, especially those with linkers and labels that are chemically divergent from the specific disulfide linker and Cy3 and Alexa Fluor labels, and those nucleotides modified at sugar or base positions.

[13] The specification also discusses another purported experiment under the section "Enzyme Incorporation of 3'-Azidomethyl dNTPs." '937 Patent at 59:12-23. Again, this experiment uses the present tense consistent with a prophetic example. Regardless, this experiment is not a working example of claim 13 of the '973 Patent. *See* Sutherland ¶ 56.

Further, the specification is silent on how variables such as the base location, linker size and type, label size and type, and other modifications of nucleotides impact incorporation. *See* Sutherland ¶60. While the specification identifies the need to select an enzyme (such as a polymerase) to effect incorporation of 3'-O-azidomethyl blocked nucleotides, it does not teach how to do so. '973 Patent at 18:59-19:6. Indeed, the specification does not describe any incorporation efficiency for any enzyme for any 3'-O-azidomethyl blocked nucleotide. *See* Sutherland ¶57. Nor does it teach how to select an enzyme, what amino acids to mutate, and what conditions to choose (temperature, pH, buffer composition) to accomplish the incorporation efficiency required for an adequate read length. *See* Sutherland ¶61.

Moreover, there is no example of monitoring any 3'-O-azidomethyl blocked nucleotides by any non-radioactive means, much less by fluorescent means. *See* Sutherland ¶62. In fact, as discussed above, three of the four 3'-O-azidomethyl blocked and labeled nucleotides have an identical Cy-3 fluorescent label. '444 Patent at 27:30-58 (structure 6); 49:1-29 (structure 24); 57:30-54 (structure 32). There is no monitoring method that could resolve these three nucleotides based on the same Cy-3 fluorescent label.

Finally, the specification of the '973 Patent provides no suggestion or teaching whatsoever on how to use ***un***labeled nucleotides in sequencing methods, which is CGI's CoolMPS innovation. *See* Sutherland ¶58. Only after years of independent research—well after the filing of the '973 Patent—did CGI develop this novel, pioneering technology that does not require a labeled nucleotide and implemented it in an efficient and accurate MPS platform. Ex. D16.[14]

The relevant field was nascent and unpredictable in 2002-2003. Dr. Burgess testified that the field of SBS was "relatively new" in the 2002-2003 timeframe. Ex. D23 at 162:15-20; *see also*

[14] The '973 Patent stems from a PCT application (PCT/GB2003/003686) filed on August 22, 2003. '973 Patent at 1:9. The PCT application claims require "detecting the label linked to the base," which is not used by CoolMPS (because it does not employ any labeled nucleotide, much less any based-linked label or the detection thereof). Ex. D24 at 122. To capture CoolMPS, Illumina, in a preliminary amendment following the filing of the PCT application in the PTO, deleted that requirement under the guise of "conform[ing] claims more closely to U.S. practice," but without pointing to any support in the specification for use of unlabeled nucleotides. Ex. D28 at claims at 8. While Illumina succeeded in blinding the PTO examiner, the expansion of the claims far beyond anything actually invented exacerbates the invalidity defects raised herein.

Sutherland ¶¶67-68.[15] Specifically, Dr. Burgess identified four stringent requirements of a suitable modified nucleotide for use in SBS: the modified nucleotide must be "tolerated by polymerase [*i.e.*, the enzyme that incorporates the modified nucleotide], spectroscopically distinct for each base, stable during the polymerization phase, and deprotected efficiently under mild conditions in aqueous solution." *Id*. at 89:9-13 (referring to Ex. D29 at 4259). Dr. Burgess admitted that while the '973 and '444 Patents "solve some of these problems," these stringent requirements continued to be "formidable obstacles" at the time of the '973 and '444 Patents. *Id*. at 90:12-22. Indeed, "still today it is difficult to find nucleotide derivatives that will satisfy all these parameters at once." *Id*. at 90:25-91:2.

Dr. Burgess explained why it is still difficult to find a suitable modified nucleotide that will be incorporated by a polymerase today. He testified that incorporation by a polymerase is a process that "can be disrupted in several ways." *Id*. at 32:2-4. A "small modification [of a nucleotide] can have a big impact" on incorporation by a polymerase. *Id*. at 34:6. For example, a modification at the 2' position of the sugar and base position could interfere with incorporation by a polymerase. *Id*. at 30:1-4, 31:1-5. In fact, a base analog of a nucleotide could "prevent" incorporation by a polymerase altogether. *Id*. at 30:12-20. Similarly, if a detectable label "were added at an inappropriate place," "it might prevent incorporation." *Id*. at 31:7-13. And "[i]f the label were added in a way that incorporation was still allowed, then the presence of the label might influence further incorporation step." *Id*. at 31:13-16. Moreover, the linker interferes with the incorporation by a polymerase. *Id*. at 31:18-23. In fact, Dr. Burgess's own research in 2003 revealed that "[t]he linker had a profound effect on the incorporation" of a modified nucleotide. Ex. D30 at 4608." When asked to explain this finding, Dr. Burgess, who considered himself a person of "extraordinary skill in the art," did not know the "exact reason." Ex. D23 at 77:15-18; 117:8-13.

Further, to achieve a longer read length, incorporation efficiency—not just whether incorporation will occur—becomes critical. A 2005 review article on SBS discusses the relationship between read length and reaction efficiency: achieving a read length of 7, 14, 35, 69, 149, and 693 bases requires a cycle efficiency of 90%, 95%, 98%, 99%, 99.5%, and 99.9%, respectively. Ex. D31

[15] Dr. Burgess was active in the field of SBS in the 2002-2003 time frame and has served as an expert for Illumina on multiple occasions.

at 1773. Thus, as read length increases, the incorporation efficiency requirement also increases. Consistent with this relationship, the specification teaches that "[i]n order to be of practical use, the entire process should consist of high yielding, highly specific chemical and enzymatic steps to facilitate multiple cycles of sequencing." '444 Patent at 1:61-63. Similarly, Dr. Burgess testified that in addition to being incorporated by a polymerase, a polymerase must incorporate the modified nucleotide with "high fidelity." Ex. D23 at 91:16-17.

Illumina's own data generated in 2015 demonstrates considerable variability regarding the level of incorporation between different polymerases using the same 3'-O-azidomethyl blocked nucleotide. *See* Sutherland ¶¶73-84. Not surprisingly, Illumina's expert for the prior proceedings, Dr. Romesberg, characterized the interaction of modified nucleotides with polymerases as "unpredictable." Ex. D32 at 71:6-25. Dr. Romesberg further emphasized that several different factors affect the ability for any given enzyme to incorporate a new nucleotide analogue, including properties like specific dimensions, H-bonding, ionic charge, polarity and flexibility. *Id*. at 72.

Experimental process would have been arduous and time consuming. ***First***, making new 3'-O-azidomethyl blocked nucleotides different than those eight nucleotides described in the specification would likely have been difficult. *See* Sutherland ¶¶85-91. For example, in 2003 (close to the August 2003 priority date of the '444 and '973 Patents), Dr. Burgess published an article, detailing the synthesis of Compounds 1-3, which were modified nucleotide with three linkers with various length and a fluorescent label (fluorescein) for SBS purposes. Ex. D30 at 4605. While Compounds 1-3 were not 3'-O-azidomethyl blocked nucleotides, Dr. Burgess testified that it would (1) take months of work in the lab to make 3'-O-azidomethyl equivalents of Compounds 1-3, if even possible, (2) experimentation would be necessary to determine whether those 3'-O-azidomethyl blocked nucleotides would be incorporated by a polymerase, and (3) the amount of experimentation would vary on case-by-case basis:

> Q. Now have you tried to make the 3'-azidomethyl equivalent of compounds 1 through 3 [of Ex. D30 at 4605]?
> A. No.
>
> Q. Would that be difficult to do?
> A. ***It would take months of work in the lab, and not all researchers could do it***. It would take someone with expertise.

> Q. And even …after that difficult work of making the 3'-azidomethyl equivalents on compounds 1 through 3, would you be able to tell whether those compounds would be incorporated by a DNA polymerase?
> A: …***it would be necessary to do some experimentation. How much experimentation would be necessary varies on a case to case basis***.

Id. at 118:13-119:3 (emphases added). In 2006—after the August 2003 priority date of the '444 and '973 Patents, Dr. Burgess published another article, describing two modified nucleotides with different linkers for SBS (Compounds 1 and 2). Ex. D33 at 3903. While Compounds 1 and 2 were not 3'-O-azidomethyl blocked nucleotides, Dr. Burgess, despite intimate knowledge of the patents-in-suit, testified that he did not know how long synthesis would take to make 3'-O-azidomethyl blocked nucleotides using the same linkers as in those compounds. Ex. D23 at 127:11-16.

The number of 3'-O-azidomethyl nucleotides needed to be made and screened for potential incorporation by a polymerase increases with longer read length because, as discussed above, the requisite incorporation efficiency increases as the read length increases. *See* Sutherland ¶¶92-96. The systematic screening process would also entail the synthesis of mutated polymerases, which alone would be arduous and time consuming. For example, it was not until 2005—years after the priority date of the'973 and '444 Patents—that read lengths of roughly 20 base pairs was achieved using 3'-O-azidomethyl modified nucleotide. Sutherland ¶67. Through years of innovative and extensive research and development, CGI accomplished a read length of at least 100 base pairs for the CoolMPS products. Ex. D16 at Abstract. Even finding a suitable monitoring system would have required extensive experimentation. *See* Sutherland ¶95.

The Federal Circuit's recent opinion in *Enzo* is particularly instructive. *Enzo Life Sci.*, 928 F.3d at 1340. There, the claim at issue encompassed all phosphate-labeled polynucleotides that were hybridizable and detectable. *Id*. at 1346. The claim did not restrict the chemistry used to attach the label, the chemical linker used, or the number, type, or location of the labels within the polynucleotide. *Id*. at 1347. The specification only sparingly taught how such variables would or would not impact the hybridizability and detectability of the phosphate-labeled polynucleotides and described at best one working example. *Id*. at 1347. The number of possible polynucleotides that fell within the claim was at least "tens of thousands." *Id*. at 1349. And one could not predict which phosphate-labeled polynucleotides would be hybridizable and detectable. Thus, each phosphate-

labeled polynucleotide would need to be tested to determine whether it was hybridizable and detectable. *Id*. at 1348. The Federal Circuit found that undue experimentation would be required in light of the number of tested embodiments, and affirmed the district court's summary judgment of non-enablement. *Id*. at 1349; *see also Idenix*, 941 F.3d at 1155-60 (affirming grant of JMOL on non-enablement in light of the at least hundreds of thousands of 2'-methyl-up nucleosides that meet the claim limitation, narrow working examples disclosed in the specification, and unpredictability of the art); *Wyeth*, 720 F.3d at 1385-86 (affirming summary judgment on grounds of non-enablement because the systematic screening process using routine assays constituted undue experimentation).

Here, the millions of 3'-O-azidomethyl blocked nucleotides covered by claim 3 of the '444 Patent and claim 13 of the '973 Patent far exceed the tens of thousands of polynucleotides in *Enzo*, *Idenix*, and *Wyeth*. Yet, as discussed above, the specification of the '444 Patent discloses a total of four 3'-O-azidomethyl blocked and labeled nucleotides: one label, one linker for each of the four nucleotides (A, T, C, G). The specification, however, does not provide sufficient teaching on how to make 3'-O-azidomethyl blocked nucleotides structurally different than the four 3'-O-azidomethyl blocked nucleotides made by the inventors of the '444 and '973 Patents (such as using those linker and labels described in Dr. Burgess's own publications). As Dr. Sutherland opined, synthesizing chemically divergent 3'-O-azidomethyl blocked nucleotides would have been challenging, if at all possible, in the 2002-2003 timeframe. *See* Sutherland ¶¶85-91. Indeed, as discussed above, even Dr. Burgess himself testified that "not all researchers" could make 3'-O-azidomethyl blocked and labeled nucleotides. Even for Dr. Burgess, who has been an extraordinary person skilled in the art and intimately familiar with the claimed invention, it would have taken "months in the lab" to make just three 3'-O-azidomethyl blocked nucleotides with the linkers and label he had used before. Ex. D23 at 118:3-19. For two other linker and label combinations he had used before, he did not even know how long the synthesis would take to make 3'-O-azidomethyl blocked nucleotides. Ex. D23 at 127:11-16. Thus, given the millions of the 3'-O-azidomethyl blocked nucleotides covered by claim 3 of the '444 Patent, the length of time required to make even a small number of the claimed compounds, and the uncertainty in whether certain claimed compounds could be made and how long it would have taken to make them, the full scope of claim 3 of the '444 Patent cannot be enabled.

With respect to claim 13 of the '973 Patent, the specification fails to provide a single working example of the claimed sequencing method. *See* Sutherland ¶¶92-96. Further, the specification provides no meaningful guidance on how to select, among numerous possibilities, the type of nucleotide analogs, the type of detectable labels, or the type of linkers that would be incorporated by a polymerase and would be incorporated at an efficiency level required for the desired read length. Nor does the specification teach how to choose a polymerase, where to mutate that polymerase to accomplish the incorporation efficiency required for an adequate read length with any particular 3'-O-azidomethyl blocked nucleotides. Nor does not specification provide any disclosures on how to monitor the incorporation of labeled or unlabeled nucleotides by any non-radioactive means.

In sum, like in *Enzo*, *Idenix*, and *Wyeth*, the breadth of claim 13 of the '973 Patent, the lack of any meaningful guidance in the specification, the unpredictable nature of the field, and the laborious processing in making and screening 3'-O-azidomethyl nucleotides not only raise substantial questions of non-enablement, but in fact render claim 13 of the '973 Patent not enabled as a matter of law. By choosing such broad claim language, Illumina put itself "at the peril of losing any claim that cannot be enabled across its full scope of coverage." *MagSil*, 687 F.3d at 1381.[16]

b. **The Asserted '444/'973 Claims are Anticipated or Obvious**

Given Illumina's overreaching patent prosecuting strategies, certain embodiments within claim 13 of the '937 Patent and claim 3 of the '444 Patent that are invalid under 35 U.S.C. § 102 (anticipation) and/or § 103 (obviousness). A claim is anticipated if each and every element of the claim is found in a single prior art reference. *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). A claim "is obvious if a skilled artisan would have been motivated to combine the teachings of the

[16] It should be noted that for all of the above reasons that claim 13 of the '973 Patent is not enabled, the specification of the '973 Patent also fails to provide adequate written description of the claimed invention (which, among many things, covers monitoring sequential incorporation using a mixture of unlabeled nucleotides). *See AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-01 (Fed. Cir. 2014) (A purpose of the written description requirement is to prevent "[t]he evil . . . if [a patentee] claims more than he has invented, [thereby] prevent[ing] others from attempting to improve upon the manner and process which he has described[.]"); *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1340 (Fed. Cir. 2013) (finding inadequate written description where the specification "provided two examples with empirical data confirming the enhanced stability . . . [but] [n]o such data were disclosed regarding the activity or thermostability of any of the seventeen positions that had been identified though rational design").

prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *NantKwest, Inc. v. Lee*, 686 F. App'x 864, 867 (Fed. Cir. 2017) (internal citations omitted). To invalidate a broad genus for anticipation or obviousness, ***only one species must be anticipated or obvious***. *See, e.g., Brown*, 265 F.3d at 1351.

c. **Claim 3 of the '444 Patent is anticipated**

Although Illumina repeatedly touts its "patented azido chemistry," ***Illumina did not invent the azidomethyl blocking group***. Indeed, two prior art publications (Zavgorodny 1991 and Zavgorodny 2000) each anticipate claim 3 of the '444 Patent under 35 U.S.C. § 102(b).[17] *See* Sutherland ¶¶105-108. The '444 Patent is a composition claim directed to a 3'-O-azidomethyl blocked nucleo*tide*. Zavgorodny 1991 and 2000, however, disclosed this very same 3'-O-azidomethyl blocking group on the very same 3'-position of a nucleo*side*, which meets every other limitation of claim 3. *See id.*; Ex. D35 at 7594; Ex. D36 at 1981. The only dispute regarding whether Zavgorodny 1991 and 2000 anticipate claim 3 of the '444 Patent is a claim construction issue: whether the term "nucleotide" in claim 3 of the '444 Patent encompasses a "nucleoside." Because Illumina has repeatedly represented that a "nucleotide" in the claims of the related '537 Patent is interchangeable with a "nucleoside" as defined by the '537 Patent, and there is no difference between the definition of a "nucleotide" in the '537 and '444 Patents, the term "nucleotide" should include a "nucleoside" in the '444 Patent.

First, while the ordinary meaning of a "nucleotide" is a "nucleoside" with a 5'-phosphate group, the specification of the '537 Patent sets forth a special definition for a "nucleotide" that includes a "nucleoside." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (The specification "may reveal a special definition given to a claim term by the patentee that differs from

[17] While Zavgorodny 1991 was considered by the Examiner during prosecution of the '444 Patent, Illumina is not entitled to deference because the Examiner never cited Zavgorodny 1991 for the disclosure of azidomethyl. Rather, the Examiner cited Zavgorodny 1991 for the disclosure of a -CH_2F protecting group, and the pending claim did not even include azidomethyl at that time. *See* Ex. D34 at 2-3. In response, Illumina amended the claims to remove the -CH_2F protecting group which Zavgorodny 1991 disclosed, removed the word "nucleoside," knowing that its broad claim constructions would nonetheless capture nucleosides, and then added the azidomethyl protecting group. *See* -1465 D.N. 14-5 at 2. The Examiner never specifically found the claims to be patentable over a nucleoside having the claimed 3'-O-azidomethyl protecting group. *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1261-62 (Fed. Cir. 2012) (Federal Circuit vacating preliminary injunction because the District Court "incorrectly rejected [Defendants'] substantive arguments" because both cited references "were before the PTO during prosecution.").

the meaning it would otherwise possess" and "[i]n such cases, the inventor's lexicography governs."). In particular, the specification defines a "nucleotide" as "consisting of a nitrogenous base, a sugar, and one or more phosphate groups" and further defines a "nucleotide" as encompassing a "derivative" and "analogue" of the nucleotide. '537 Patent at 4:48-49, 5:17-20. The specification then defines a "derivative" or "analogue" as a "compound or molecule whose core structure is the same as, or closely resembles that of, a parent compound [*i.e.*, a nucleotide] but which has a ***chemical*** or physical ***modification***…." '537 Patent at 5:1-4 (emphases added). Dr. Burgess readily admitted that "[r]emoving a group is a chemical modification." Ex. D23 at 72:14-16. A removal of the 5'-phosphate group of a nucleotide results in a "nucleoside," rendering a "nucleoside" a "derivative" or "analog" of a "nucleoside." Thus, a "nucleoside" falls within the special definition of "nucleotide" in the '537 Patent (*i.e.*, as a "derivative" or "analog" of a "nucleotide."). Consistent with this construction, Illumina has repeatedly represented that the '537 Patent "uses the terms 'nucleotide' and 'nucleoside' interchangeably." *See* Ex. D37 at 11, 13-14.

Second, the '444 Patent shares a common priority application (U.S. Patent Application Serial No. 10/227,131 filed on August 23, 2002) with the '537 Patent and has the same special definitions of a "nucleotide," "derivative," and "analog" as the '537 Patent. *See* '444 Patent at 1:13-15, 14:11-12, 14:33-39, 14:51-53. Thus, the patentee has again acted as its own lexicographer in the '444 Patent—in an identical way as the '537 Patent. There is no reason why the scope of a "nucleotide" in the '444 Patent should be any different than that in the '537 Patent. Even Dr. Burgess agreed that "there is no obvious reason" to have different meanings of the same term across the same family of patents. Ex. D23 at 47:19-48:1. Not surprisingly, Dr. Burgess did not propose any different definition for a "nucleotide" in the '444 Patent. *See* -3770 D.N. 87-1 ¶48 (definition of "nucleotide" for the '537 Patent); -1465 D.N. 13 ¶48 (no new definition of "nucleotide" for the '444 Patent). Thus, a "nucleotide" is also used interchangeably with a "nucleoside" in the '444 Patent. A "nucleoside" thus falls within the scope of a "nucleotide" in the '444 Patent (again as a "derivative" or "analog" of a "nucleotide" as in the '537 Patent).

Third, Illumina did not exclude "nucleoside" from the special definition of "nucleotide" during the prosecution of the '444 Patent. Although Illumina did remove the word "nucleoside"

from the claims during prosecution, it cannot show that this was an unambiguous disavowal of "nucleoside" from the scope of "nucleotide." Ex. D38 at 2. Specifically, during prosecution of the '444 Patent, Illumina stated that (1) "[c]laim 1 [which matured into claim 1 of the '444 Patent] is amended to be directed to a modified nucleotide having the recited features," (2) Zavgorodny 1991 "do[es] not teach or suggest a compound of instant claim 1" and "fail[s] to anticipate the claimed nucleotide." *Id*. at 7 (emphasis original). Because the Examiner cited Zavgorodny 1991 for the disclosure of a -CH_2F protecting group, and in response, Illumina removed the -CH_2F protecting group from then pending claim 1 (which did not include 3'-O-azidomethyl), Illumina distinguished then pending claim 1 from Zavgorodny 1991 based on the removal of -CH_2F protecting group. *See* Ex. D34 at 2-3; -1465 D.N. 14-5 at 2. Illumina never stated that Zavgorodny 1991 was directed to a nucleoside or that the claim scope of "nucleotide" excluded a nucleoside. At a minimum, Illumina's amendment and accompanying arguments surrounding the removal of the word "nucleoside" are subject to multiple reasonable interpretations, which precludes clear disavowal of a "nucleoside" from the scope of a "nucleotide" in claim 3 of the '444 Patent. *Mass. Inst. of Tech. v. Shire Pharm., Inc.*, 839 F.3d 1111, 1119 (Fed. Cir. 2016) (no "clear and unmistakable" disavowal because of multiple reasonable interpretations); *see also Fujifilm Corp. v. Motorola Mobility LLC*, No. 12-CV-03587-WHO, 2015 WL 757575, at *20-21 (N.D. Cal. Feb. 20, 2015).

In sum, because a "nucleoside" falls within the special definition of a "nucleotide" in the '444 Patent, the " nucleoside" in Zavgorodny 1991 and 2000 is a "nucleotide" defined by the '444 Patent and claim 3 is therefore anticipated by Zavgorodny 1991 and 2000. *See* Sutherland ¶¶105-108. At a minimum, these two references present a substantial question of novelty of claim 3 of the '444 Patent.

d. **Claim 3 of the '444 Patent is obvious**

Even if Zavgorodny 1991 and 2000 do not anticipate claim 3 of the '444 Patent, they alone (or in combination with other references) render it obvious. To the extent that the term "nucleotide" is construed to exclude a nucleoside, the only difference between Zavgorodny 1991 and 2000 is the addition of one or more phosphate groups to the 5'-OH on the ribose (Zavgorodny 2000) or deoxyribose sugar (Zavgorodny 1991). *See* Sutherland ¶109.

With respect to the motivation to add a phosphate to the 5'-OH of a nucleoside, Zavgorodny 1991 alone specifically states that the disclosed azidomethyl blocked nucleosides are useful as "synthons." Ex. D35 at 7595. Dr. Burgess explained that a "synthon" is "a molecule that a chemist would use as a building block in an organic synthesis" "to make another" molecule. Ex. D23 at 163:4-11. The most common use of a nucleoside as a building block is for the synthesis of a nucleotide, as nearly every chemical synthesis of a nucleotide is achieved via phosphorylation of the 5'-OH of the corresponding nucleoside. Sutherland ¶¶112, 114. A POSITA would be motivated to convert Zavgorodny 1991's 3'-O-azidomethly blocked nucleosides into nucleotides for a variety of applications, including use in the studies of enzymatic reactions or organic chemistry. *Id.* Indeed, Dr. Burgess himself began adding a phosphate to the 5'-OH of a nucleoside in the 1990s—over a decade prior to the priority date of the '444 Patent. Ex. D23 at 56:21-25; 58:23-59:10. His motivation was to "test with polymerase enzyme" because a nucleoside (without a 5' phosphate group) is not a substrate for a polymerase and a nucleotide (with a 5' phosphate group) is a substrate for a polymerase. *Id.* at 57:9-10, 57:21-58:1, 58:23-59:10, 60:18-19. Dr. Burgess also explained another motivation to add a 5' phosphate to the 5'-OH of a nucleoside is "a chemist wanting to demonstrate a superior method to generate triphosphate in general." *Id.* at 61:6-7. Further, a POSITA in the art would be motivated to combine Zavgorodny 1991 with the 5'-phosphorylation method taught in Haitt to render claim 3 of the '444 Patent obvious. Sutherland ¶113; Ex. D39.

With respect to Zavgorodny 2000, which discloses an RNA version of the 3'-O-azidomethyl nucleoside molecule (as opposed to the DNA version of 3'-O-azidomethyl nucleoside molecule in Zavgorodny 1991), Dr. Burgess testified that the motivation to add a 5' phosphate applied to both DNA and RNA. Ex. D23 at 65:25-66:8. Further, Zavgorodny 2000 states that the 3'-azidomethyl blocked nucleosides would be useful as "antivirals," which would motivate a POSITA to convert them into nucleotides for enzymatic testing. For example, one antiviral drug known in the 1990s is AZT (azidothymidine), which treats the HIV infection. Dr. Burgess testified that "when AZT enters a cell[,] it is phosphorylated by enzyme in the cell," which is "incorporated into a growing DNA strand by an enzyme." Ex. D23 at 145:12-17. Such knowledge was known in the 1990s. *Id.* 147:5-8. Further, a POSITA in the art would be motivated to combine Zavgorodny 2000 with *in vitro*

studies using 5'-phosphorylated AZT taught in Kerr to render claim 3 of the '444 Patent obvious. Sutherland ¶115; Ex. D74.

Techniques for converting nucleotides to nucleosides were well known at the time of priority of the '444 Patent (August 22, 2003), and a POSITA would have a reasonable expectation of success using these techniques. Sutherland ¶¶117-119. As Dr. Burgess testified, the "general method of adding phosphate groups to the 5' position of nucleosides predated" his research in the 1990s. Ex. D23 at 57:17-19; 65:18-24. In sum, Zavgorodny 1991 and 2000 alone or in combination with other references render or at least raise a substantial question that claim 3 of the '444 Patent is obvious.

e. **Claim 13 of the '973 Patent is obvious**

The combination of Parce and Zavgorodny 1991 renders claim 13 of the '973 Patent obvious. *See* Sutherland ¶¶120-133. Parce discloses a sequencing method using 3'-O-blocked nucleotides, which includes every claim 13 limitation except the 3'-O-azidomethyl blocking group. *Id.* at 120.

One of ordinary skill would have been motivated to select Zavgorodny 1991's 3'-O-azidomethyl group as a replacement for Parce's blocking groups (a 3'-phosphate and a disulfide). Parce uses TCEP to deprotect the disulfide-based blocking groups. Ex. D42 at 15:56-59; Sutherland ¶¶122-125. Zavgorodny 1991 specifically states that the "azidomethyl group is of special interest since it can be removed … with triphenylphosphine," an agent closely related to Parce's TCEP that reduces azides in the same manner as TCEP. Ex. D35 at 7595. One of ordinary skill in the art would have expected Zavgorodny 1991's 3'-O-azidomethyl to be cleaved rapidly and efficiently in Parce's sequencing method. It was generally known in the art that TCEP rapidly and efficiently reduces azides on nucleotides and sugar moieties, such as those disclosed in Zavgorodny 1991, even at room temperature. Sutherland ¶¶128-133; Ex. D45 at 3229.

One of ordinary skill would also have been motivated to select Zavgorodny 1991's 3'-O-azidomethyl group as a replacement for Parce's carbamate blocking groups. Sutherland ¶¶126-127. Zavgorodny 1991's 3'-O-azidomethyl group is much smaller than the carbamate blocking groups disclosed in Parce, which would have motivated a POSITA to use Zavgorodny 1991's 3'-O-azidomethyl group with Parce's sequencing method. Further, while the carbamate moiety was known to interfere with polymerase action, Zavgorodny 1991's 3'-O-azidomethyl group would be

more stable during incorporation. Thus, one of ordinary skill would have expected Zavgorodny 1991's 3'-O-azidomethyl group to be more stable during incorporation than Parce's carbamate blocking groups. Sutherland ¶¶128-133.

In sum, the combination of Parce and Zavgorodny 1991 renders claim 13 of the '973 Patent obvious or at least raises a substantial question of obviousness.

f. **The Asserted '025/'200/'537 Claims Are Not Enabled**

For essentially the same reasons discussed with respect to the non-enablement of claim 13 of the '973 Patent and claim 3 of the '444 Patent, the asserted claims of the '025, '200, and '537 Patents are not enabled. Indeed, the asserted claims of the '025, '200, and '537 Patents are even less enabled because (1) the priority date of these claims is August 23, 2002 and the relevant field was even less predictable in August 2002 than in August 2003 (the priority date of the '444 and '973 Patents) and (2) specification of the '025, '200, and '537 Patents contains even less relevant disclosure with no synthesis of any 3'-O-azidomethyl blocked nucleotides or any example (paper or working) of using 3'-O-azidomethyl blocked nucleotides in a sequencing method. Sutherland ¶¶134-138.

B. Illumina Will Not Suffer Irreparable Harm

Illumina has fallen far short of the requisite "'***clear showing***' that it is at risk of irreparable harm, which entails '***a likelihood of substantial and immediate irreparable injury***.'"[18] Blackburn ¶¶6-46; Smith ¶¶144-148; Rogers ¶¶4-19. Illumina presents only speculation of its Commercial Director Mr. Van Oene, who unreasonably asserts that even a single sale by Defendants in the U.S. would cause irreparable harm. Ex. D49 at 193:2-195:20. But numerous courts have found such conclusory and unsupported arguments insufficient to demonstrate a likelihood of irreparable harm.[19]

[18] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1325 (Fed. Cir. 2012) (emphasis added); *see also Winter*, 555 U.S. at 22 ("[A] preliminary injunction will not be issued simply to prevent the possibility of some remote future injury.").

[19] *Winter*, 555 U.S. at 22; *Automated Merch. Sys., Inc. v. Crane Co.*, 357 F. App'x 297, 301 (Fed. Cir. 2009) ("[L]ost market share must be proven (or at least substantiated with some evidence) in order for it to support entry of a [PI], because granting [PIs] on the basis of speculative loss of market share would result in granting [PIs] 'in every patent case where the patentee practices the invention.'" (citation omitted); *Beats Elecs., LLC v. Fanny Wang Headphone Co., Inc.*, No. C-10-5680 MMC, 2011 WL 31198, at *3 (N.D. Cal. Jan. 5, 2011) (finding evidence cited by plaintiff was

(Footnote Cont'd on Following Page)

Illumina also argues that Illumina and Defendants are "direct competitors," but fails to show how that leads to irreparable harm. Courts have recognized that simply being a "direct competitor" does not mean that irreparable harm will ensue.[20] In fact, given that MGI Americas is [redacted] Ex. D89; Blackburn ¶14 citing (-1465 D.N. 12-32 at 8 and D89). Moreover, neither of MGI's systems are approved for U.S. clinical use, further reducing the potential for immediate harm. Ex. D49 at 65:23-69:9.

Illumina also fails to account for the fact that in the U.S. market MGI Americas will be a nascent competitor and is unlikely to make a noticeable dent in Illumina's dominant market position prior to trial. Blackburn ¶28; Smith ¶¶149-152. In fact, [redacted] Illumina's 2019-2021 strategic plan states that Illumina [redacted] Ex. D46 at ILMNBGI0032447; *id.* at ILMNBGI0032434 ([redacted]. Illumina's internal analysis is consistent with MGI Americas' experience launching its products in Canada, where [redacted]

insufficient to demonstrate a likelihood of irreparable harm in part because the "evidence [was] wholly conclusory in nature").

[20] *See Standard Innovation Corp. v. Lelo (Shanghai) Trading Co.*, No. 15-cv-04858-BLF, 2015 WL 6828317, at *3 (N.D. Cal. Nov. 6, 2015) (noting that status as a direct competitor without further evidence is not enough to show irreparable harm)); *MMJK, Inc. v. Ultimate Blackjack Tour LLC*, 513 F. Supp. 2d 1150, 1156-1158 (N.D. Cal. 2007) (same).

[redacted]. Rogers ¶8-12.

MGI Americas' own launch plan for the U.S. show that its "revenue goal" is [redacted]. Ex. D75 at CGI000043149-165. Even if MGI Americas were to meet these goals, that would amount to only [redacted] of Illumina's 2019 U.S. revenue. *See id.*; Ex. D93 at 43. This amounts to a goal of [redacted] in 2020, compared to Illumina's estimate that there are approximately [redacted] Ex. D52 at ILMNBGI1066641; Ex. D49 at 43:9-44:5 ([redacted]). Moreover, Illumina admits that (i) it "is a recognized industry leader in DNA sequencing, and its technology is used to generate over 90% of the world's sequencing data" despite competing against Defendants outside of the United States and (ii) "sequencing customers tend to show significant loyalty to their initial supplier and are reluctant to change sequencing instruments once they become accustomed to them." -1465 D.N. 11 at 21-22 (Mot.). Thus, given the huge disparity between MGI Americas' "revenue goal" as a nascent competitor and Illumina's dominant role in the market, Illumina cannot show that it would immediately and irreparably lose substantial market share or business opportunities as a result of activities prior to trial.

Illumina's claim that it will suffer price erosion is not supported by any evidence that any reduction in price is likely to occur, or even if prices were temporarily reduced, that they would not be reversible.[21] *See* Ex. D49 at 80:14-81:3. There is no evidence that Illumina intends to lower its prices as a result of MGI Americas' activity in the U.S.; [redacted]. *See* Ex. D48 at ILMNBGI1085328 ([redacted]; Ex. D49 at 77:24-79:19. Moreover, while Illumina argues that it

[21] *See Automated Merch. Sys.*, 357 F. App'x at 301 (holding the district court clearly erred by finding irreparable harm because evidence of lost sales could not support finding of irreparable harm "no matter how much evidence of lost revenue [plaintiff] presented" and neither the district court nor the plaintiff cited evidence of price erosion); *Mike's Train House, Inc. v. Broadway Ltd. Imports, LLC*, 708 F. Supp. 2d 527, 532 (D. Md. 2010) ("Because potential lost sales revenue is compensable through damages, evidence of such losses is insufficient by itself to support a finding of irreparable harm. Similarly, price erosion-without evidence that the patentee would be *entirely* forced out of the market by the infringer's lower prices-is not irreparable harm.")

has had to offer lower prices in China to compete with Defendants (Van Oene ¶71), it offers no evidence of this or its relevance to the U.S. market, [redacted] Ex. D50 at ILMNBGI1098497-501; Blackburn ¶¶36-39. Due to Illumina's practice of using long-term contracts and sole-source tenders, MGI Americas' potential sales in the U.S. would have little, if any, impact on Illumina's pricing. Ex. D49 at 201:9-204:20.

Even if Illumina were to reduce its prices due to additional competition, it is unlikely to suffer any harm due to the elasticity of demand in the sequencing market. Ex. D52 at ILMNBGI1066636 ("[redacted]"); -1465 D.N. 12-4 at 22 (Van Oene, Ex. D); Blackburn ¶33. Such market growth implies additional revenue growth for Illumina, even if prices were to decrease. Thus, additional competition in the market will have the beneficial effect of expanding access to these fundamental technologies while having little (if any) impact on Illumina.

Similarly, Illumina fails to demonstrate that reputational harm is likely. Given that Illumina is the dominant market player and has been for nearly a decade, its reputation is already solidified and is unlikely to be impacted by Defendants' activities. Blackburn ¶26-30. Defendants also are already well-known in the sequencing market, particularly outside of the U.S., such that their geographic expansion is unlikely to have any impact on Illumina's reputation. Blackburn ¶¶28-29.

1. Monetary Damages are Adequate to Compensate for Any Alleged Harm.

Illumina fails to demonstrate that the remedies available at law, including monetary damages, would be inadequate to compensate for its alleged injury.[22] Any alleged harm suffered by Illumina as a result of Defendants' activities is readily quantifiable. Blackburn ¶¶31-39. Illumina is a sophisticated entity that performs market research and analysis from which any damages could be quantified. *See* Blackburn ¶¶34-39. Moreover, since Illumina is currently the ***only*** competitor in the U.S. market for mid- and high-throughput sequencers (Ex. D49 at 30:13-32:16), it will be straight forward to demonstrate the extent to which Illumina loses any sales or lowers prices in response to Defendants' activities. Blackburn ¶39. As noted in *MMJK, Inc*, 513 F. Supp. 2d at 1157, "the presence of only two legal competitors seriously undercuts plaintiff's argument that it will not be

[22] *See eBay, Inc. v. MercExchange, LLC*, 547 U.S. 388, 391 (2006).

able to recapture market share, and strongly suggests that damages will be a sufficient remedy should defendant later be found to infringe."

2. No Causal Nexus Between Alleged Harm and Alleged Infringement.

Illumina also completely fails to establish that a "sufficiently strong causal nexus relates the alleged harm to the alleged infringement" to justify an injunction.[23] "To show irreparable harm, it is necessary to show that the infringement ***caused*** harm in the first place. Sales lost to an infringing product cannot irreparably harm a patentee if consumers buy that product for reasons other than the patented feature."[24] Illumina completely fails to address the causal nexus requirement, no doubt because Defendants' sequencing products have advantages over Illumina's products that are unrelated to the claimed features. For example, with both StandardMPS and CoolMPS sequencing reagents, Defendants' sequencers use DNA nanoballs ("DNBs") that rely upon linear amplification of a single target DNA and are therefore inherently less error-prone than Illumina's PCR-based method that relies on making copies of copies. Rogers ¶5-6; Smith ¶33, 100-119; -1465 D.N. 12-20 at 12 (Van Oene, Ex. T). By avoiding use of PCR for amplification, Defendants' sequencing products avoid common PCR-based errors such as false SNPs, false InDels, coverage bias, and index hopping. Rogers ¶5-7; Smith ¶101-105; -1465 D.N. 12-20 at 12 (Van Oene, Ex. T). Additionally, Defendants' CoolMPS Chemistry does not use a label attached to the nucleotide base, and therefore permits the use of additional fluorescent labels resulting in brighter signals that facilitate longer read lengths and higher throughput while using less costly sequencing reagents. Rogers ¶7; Smith ¶108-109. Consequently, consumers may prefer Defendants' sequencers over Illumina's for these advantages or for different applications. Rogers ¶17-18. Indeed, at least one of Illumina's current Canadian customers has purchased one of Defendants' sequencers because of these unique advantages of Defendants' sequencers. Rogers ¶17-19; Ex. D54.

C. Equity Weighs Heavily Against A Preliminary Injunction

The balance of the hardships favors denial of an injunction. As discussed above, there is a substantial question as to the invalidity of the asserted patents and Illumina will not be irreparably harmed by denial of an injunction. *See* Parts A-B, *supra*. In contrast, if Illumina's request for relief

[23] *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1374 (Fed. Cir. 2012).

[24] *Apple Inc.*, 695 F.3d at 1374 (emphasis added) (quoting *Apple, Inc.*, 678 F.3d at 1324).

is granted, Defendants would be prevented from continuing their ongoing R&D efforts in their San Jose, California facility—putting at least [redacted] local jobs at risk—all to prevent activities that ultimately pose no meaningful threat to Illumina's dominant market position. Zhao ¶¶4-6.

Defendants have invested over [redacted] in bringing their novel CoolMPS technology to market, an investment that would be substantially undermined if enjoined until trial. Ex. D112. Indeed, given the time expected for MGI Americas to gain meaningful traction in the market (likely years), a preliminary injunction would pose little harm to Illumina but would effectively delay MGI's market participation until years after trial. *See* Smith ¶¶149-152; Blackburn ¶¶47-49; Ex. D112. Thus, a preliminary injunction would not only have the effect of limiting MGI's market entry prior to trial, but would prevent MGI from meaningfully competing in the U.S. market long past patent expiration. *See* Smith ¶¶149-152; Blackburn ¶¶47-49; Rogers ¶12-17.

Equity also favors denying the Motions because Illumina is infringing CGI's patent rights.[25] It would be highly prejudicial to Defendants if this Court granted preliminary relief to Illumina—the market monopolist—by preventing MGI Americas' U.S. market entry while at the same time permitting Illumina to impinge upon the Defendants' patent rights. Indeed, two of the core technologies that Illumina touts for its most advanced systems (two-color sequencing and high density patterned arrays) are the subject of Defendants' patent infringement claims against Illumina. Ex. D49 at 49:10-52:3. Thus, the equities weigh strongly against an injunction in this situation.

D. The Public Interest Would Be Disserved by A Preliminary Injunction

The public interest in the advancement of innovative and affordable DNA sequencing technologies—including those that promote the public health—far outweighs any potential interest in protecting Illumina's patent rights. The sole public interest cited by Illumina in favor of an injunction is to enforce Illumina's patent rights (-1465 D.N. 11 at 25), but Defendants have shown a substantial question regarding the invalidity of the Asserted Claims (*see* Part A, *supra)*. Even if the Court were to find Illumina's asserted patents likely to be valid and infringed, the public has ***no***

[25] *Illumina, Inc. et al. v. BGI Genomics Co., Ltd et al.*, 3-19-cv-03770, D.N. 94 at ECF 37-67 (N.D. Cal. Feb. 24, 2020); *Complete Genomics, Inc. v. Illumina, Inc.*, 1-19-cv-00970, D.N. 7 (D. Del. Jul. 25, 2019).

interest in quashing competition from a nascent competitor while at the same time permitting a market monopolist to exploit the patent rights of that competitor. *See* Part C, *supra*; Ex. D17 ¶1.

"[F]or good reason, courts have refused to permanently enjoin activities that would injure the public health."[26] Defendants' sequencing products are not only useful for research and diagnosis of genetic disease, but are also used to monitor mutations to deadly pathogens (including COVID-19) on a population-wide scale. Ex. D55; Ex. D56 (describing use of DNBSEQ-T7 sequencing system "in order to decode the genome sequence of the new coronavirus, study and analyze the evolutionary sources and pathological mechanisms of the new coronavirus, and monitor the mutation of the virus at a large population level"). Because Defendants' sequencing products are very different than Illumina's—they use PCR-free amplification, unlabeled nucleotides, antibody detection methods, and unique instruments and analysis software, among other differences—they provide an important alternative approach to genomic analysis. Smith ¶100-109; Rogers ¶5-8, 17-19.

Furthermore, it is universally recognized that as WGS becomes more affordable, it will usher in a new era of personalized medicine that will advance public health. Illumina itself recognizes that "[redacted]" Ex. D52 at ILMNBGI1066560 ("[redacted]"), ILMNBGI1066561 ("[redacted]"). Currently, the only DNA sequencing technologies that are feasible and sufficiently affordable for WGS are technologies from Illumina and Defendants. *See* Ex. D49 at 30:13-32:16; -1465 D.N. 12-4 at 16 (Van Oene, Ex. D) ("[redacted]"). Rapid advancement of personalized medicine and genomic-based

[26] *Cordis Corp. v. Bos. Sci. Corp.*, 99 F. App'x 928, 935 (Fed. Cir. 2004); *see also Conceptus, Inc. v. Hologic, Inc.*, No. 09-02280 (WHA), 2012 WL 44064, at *3-4 (N.D. Cal. Jan. 9, 2012) (refusing to grant an injunction when doing so would eliminate "an important alternative for patients"); *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1458 (Fed. Cir. 1988) (affirming exclusion of test kits from the scope of an injunction because "the public interest is served best by the availability of these kits").

diagnostics depends upon access to a variety of cost-effective WGS technologies, and permitting Illumina to remain the sole provider in the U.S. has and will continue to forestall such advancement, to the detriment of the public interest. *See* Smith ¶¶120-143; Ex. D52 at ILMNBGI1066587 ([redacted]).

From an economic perspective, an injunction is also against the public interest. "[I]t is widely recognized in economics that increased competition not only enhances the economic welfare of consumers, but also the total economic welfare of society." Blackburn ¶52. Courts have also recognized the public interest in promoting competition.[27] Where, as here, Illumina can be fully compensated for any economic loss suffered due to any alleged infringement, the public interest favors competition and access to differentiated technologies. Smith ¶¶100-143; Blackburn ¶¶50-54.

III. THE SCOPE OF ILLUMINA'S PROPOSED INJUNCTION IS OVERBROAD.

Illumina's proposed injunction would prevent Defendants from continuing their R&D activities in the U.S., thereby threatening numerous researchers' jobs, despite the fact that those activities pose no threat of harm to Illumina (much less irreparable harm) and have been ongoing for years. Illumina's proposed injunction also improperly encompasses products that have no possibility of infringing the asserted patents, including sample preparation and data analysis systems, that can be used with unaccused sequencing systems. Rogers ¶20. Further, Illumina seeks an injunction against all use of StandardMPS even though Defendants only currently plan to offer it to KOLs for validation and comparison studies, which will not cause irreparable harm to Illumina. Smith ¶¶149-152. However, for many of the reasons stated above, there should be no restrictions on StandardMPS (*e.g.*, should MGI Americas decide to sell it commercially).

IV. CONCLUSION

For the reasons set forth above, Illumina's Motions should be denied.

[27] *Nano-Second Tech. Co., Ltd. v. Dynaflex, Int'l*, No. CV 10–9176 RSWL (MANx), 2011 WL 4502025, at *5 (C.D. Cal. Sept. 28, 2011); *NYKO Techs. Inc v. Energizer Holdings Inc.*, No. CV 12-03001 GAF (VBKx), 2012 WL 12882885, at *8 (C.D. Cal. June 1, 2012).

Dated: April 14, 2020

ARNOLD & PORTER KAYE SCHOLER LLP

By: */s/ Katie J.L. Scott*
Katie J.L. Scott

Attorney for Defendants
BGI AMERICAS CORP., MGI TECH CO., LTD., MGI AMERICAS, INC., AND COMPLETE GENOMICS INC.